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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/674,853	Applicant(s) Mavilio
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 26, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/2/03 has been entered. As requested, the amendment under 1.116 received on 12/26/02, has been entered. Claims 1-10 have been canceled, and new claims 11-18 have been entered. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The claims recite a method for increasing the frequency of myogenic conversion of genetically modified dermal fibroblasts. However, the method steps recite the transduction of fibroblasts, not dermal fibroblasts. Therefore, the scope of the claims is confusing as it is unclear whether the method steps as written are intended to encompass fibroblasts other than dermal fibroblasts.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Murry et al. (1996) J. Clin. Invest., Vol. 98 (10), 2209-2217. The claims recite genetically modified fibroblasts transiently expressing a muscle lineage commitment gene, wherein the gene is myoD.

Murry et al. teaches fibroblasts infected with an adenovirus encoding MyoD both *in vitro* and *in vivo* resulting in the detectable expression of MyoD (Murry et al., page 2211 and 2212). Thus, by teaching all the limitations of the claims as written, Murry et al. anticipates the instant invention.

Claim Rejections - 35 USC § 103

The rejection of claims 1-10 under 35 U.S.C. 103(a) as being unpatentable over Watt et al. in view of Choi et al. and Murry et al. is withdrawn in view of applicant's cancellation of these claims.

Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/09373, 28 March 1996, hereafter referred to as Watt et al., in view of Choi et al. (1990), PNAS, Vol. 87, 7988-7992, and further in view of Murry et al. (1996) J. Clin. Invest., Vol. 98 (10), 2209-2217. The applicant claims methods for increasing the frequency of myogenic conversion of genetically modified dermal fibroblasts comprising ex-vivo transduction of fibroblasts with a therapeutic gene, and transient transfection of the fibroblasts with a vector encoding a muscle lineage commitment gene under control of a strong promoter, wherein the vector is an adenoviral vector. The applicant further claims said methods wherein the muscle

lineage commitment gene is myoD, and wherein the rate of myogenic conversion is greater than 40%.

Watt et al. teaches the transduction of dermal fibroblasts which have been removed from a patient with a muscular disorder with a vector encoding dystrophin, a gene therapeutic for muscular dystrophy (Watts et al., page 6, and pages 23-24, claims 1-24). Watt et al. does not specifically teach the further modification of these cells with a viral vector encoding myoD. Choi et al. supplements Watt et al. by teaching that primary fibroblasts transduced with a retrovirus encoding myoD differentiate into striated mononucleated myoblasts and multinucleated myotubes *in vitro* which are indistinguishable from normal myoblasts (Choi et al., page 7988, abstract and materials and methods section, pages 7988-7989).

Both Watt et al. and Choi et al. provide the motivation for further transforming fibroblasts which encode dystrophin with a second viral vector encoding myoD. Watt et al. teaches that the preferable method of treatment of muscular dystrophy would modify the patient's own myoblasts to express dystrophin (Watt et al., pages 2-3, bridging paragraph). However, because the use of myoblasts from patients with muscular dystrophy for gene therapy of MD pose several problems because the disease myoblasts have already passed through several bouts of degeneration/regeneration, Watt proposes using transduced fibroblasts since donor fibroblasts can fuse in vivo to make a multinucleate cell which can behave like a

muscle cell (Watt et al., page 3, lines 15-22). Choi et al. solves the problem identified by Watt et al. by teaching that fibroblasts can be converted to myoblasts by expression of myoD. Thus, based on the motivation for utilizing cells that are capable of behaving like myoblasts for the therapy of MD taught by Watt et al., and the teachings of Choi et al. that transduction of dermal fibroblasts with the myoD gene results in the differentiation of the fibroblasts to actual myoblasts, it would have been *prima facie* obvious to the skilled artisan at the time of filing to co-express the myoD gene in the fibroblasts taught by Watt et al. in order to differentiate the dystrophin expressing fibroblasts into dystrophin expressing myoblasts for use in the therapy of muscular dystrophy. Further, based on the successful transduction of primary fibroblasts with viral vectors encoding dystrophin and myoD as taught by Watt et al. and Choi et al., the skilled artisan would have had a reasonable expectation of success in preparing a modified fibroblast which has been co-transduced with both the genes for dystrophin and myoD.

The teachings of Watt et al. in view of Choi et al. differ from the instant invention in that Choi et al. does not teach the use of an adenovirus to express myoD in the dermal fibroblasts. Murry et al. supplements Choi et al. by teaching the use of an adenovirus encoding myoD to infect fibroblasts *in vitro* and *in vivo* resulting in myoconversion (Murry et al., pages 2211-2212). Murry et al. further provides motivation for using the adenovirus encoding myoD over the retrovirus

encoding myoD taught by Choi et al. by teaching that fibroblasts infected with adenovirus encoding myoD demonstrated up to 14% myoconversion compared to 5% or less observed with the retrovirus taught by Choi et al. Thus, based on the increased level of myoconversion using adenovirus encoding myoD over retrovirus encoding myoD, as demonstrated by Murry et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use an adenovirus encoding myoD to infect dermal fibroblasts as taught by Choi et al., and to use those dermal fibroblasts in the methods of *ex vivo* gene therapy taught by Watt et al. Further, based on the successful use of the adenovirus encoding myoD to infect and myoconvert cardiac fibroblasts, the skilled artisan would have had a reasonable expectation of success in using the adenovirus encoding myoD to infect and myoconvert dermal fibroblasts.

Applicant's arguments as they apply to these new grounds of rejection have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons discussed in detail below.

The applicant's comments on page 3 were addressed in full in the advisory action, paper no. 9, page 2. In regards to applicant's statements that new claims 11-18 are patentable over Watt et al., in view of Choi et al., and Murry et al. (1995, FASEB) for reasons argued by applicants on pages 2-5 of the amendment filed on

7/1/02, please note that claims 11-18 have been rejected over a combination of Watt et al., Choi et al.., and Murry et al. (1996, J. Clin. Invest.).

In view of applicant's new claims, the applicant's arguments regarding the teachings of Watt et al. and Choi et al. have been re-addressed as they apply to the new grounds of rejection. The applicant is reminded however that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The applicant has argued that the methods taught by Watt et al. result in the spontaneous conversion of the transfected dermal fibroblasts to muscle cells in vivo, and that the rate of spontaneous conversion is too low to make this methodology practical for treating muscle disorders in a patient. In contrast, the applicant states that their methods result in a higher frequency of myogenic conversion than that observed by Watt et al. In response, please note that the applicant claims do not recite the treatment of muscle disorders. The instant methods are directed to methods of increasing the frequency of myogenic conversion of transduced dermal fibroblasts. Only new claim 12 recites any particular rate of myogenic conversion. Furthermore, since the claims as written do not provide any baseline for measurement of rates of myoconversion, claims 11, and 13-16 read on any rate of myoconversion. It is further noted that Watt et al. was not cited for teaching the

myoconversion of dermal fibroblasts, the essential teachings of Watt et al. are the transduction of dermal fibroblasts which have been removed from a patient with a muscular disorder with a vector encoding dystrophin, a gene therapeutic for muscular dystrophy. The applicant has not refuted that Watt et al. does in fact teach this method of genetically modifying fibroblasts. Teachings relating rates of myoconversion of fibroblasts by expression of myoD were supplied by Choi et al. and Murry et al.

The applicant further argues that Choi et al. does not supplement Watt et al. because Choi et al. teaches the use of an integrating retroviral vector and that the rate of myogenic conversion using this vector is low. As noted above, this line of reasoning is not compelling in regards to applicant's claims 11, and 13-16, since the claims as written read on any rate of myoconversion of fibroblasts. In addition, applicant's concern that Murry et al. (1995, FASEB) does not teach the frequency of myogenic conversion of the cardiac fibroblasts is no longer relevant to the instant rejection since the instant rejection relies on the teachings of Murry (1996, J. Clin. Invest.) which teaches rates of myoconversion stemming from infection of fibroblasts with adenovirus encoding myoD. Murry et al. further provides motivation for using the adenovirus encoding myoD over the retrovirus encoding myoD taught by Choi et al. by teaching that fibroblasts infected with adenovirus

encoding myoD demonstrated up to 14% myoconversion compared to 5% or less observed with the retrovirus taught by Choi et al.

Regarding the limitation of new claim 12, which recites that the rate of myogenic conversion is greater than 40%, it is noted that the adenoviral vector taught by Murry et al. is the exact same vector used by applicants in the instant invention, please see page of 8 of the instant specification which cites the Murry et al. paper as the source for an Ad5-derived, E1A-deleted adenoviral vector expressing MyoD c-DNA under transcriptional control of the RSV LTR. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). In *Titanium Metals Corp. V. Banner*, 227 USPQ 773 (Fed. Cir. 1985), the court further states that it is immaterial what properties a particular composition has or who discovered the properties because if the composition in the prior art is the same as that claimed, it must necessarily exhibit the properties. Since the adenovirus encoding myoD taught by Murry is the exact same adenovirus taught by the applicants, the recited property of a rate of myogenic conversion greater than 40% in infected dermal fibroblasts is inherent to this adenovirus. The applicant is further reminded that reliance upon inherency is not improper even though the rejection is based on Section 103 instead of Section 102. *In re Skoner et al.* 186 USPQ 80 (CCPA). Finally, note that obviousness does not

require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER